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Case Report

Rituximab-induced nonspecific interstitial pneumonia like reaction in a patient with idiopathic thrombocytopenic purpura

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ABSTRACT

Rituximab, a chimeric anti-CD20 IgG1 monoclonal antibody, is an effective treatment for haematological autoimmune diseases such as idiopathic thrombocytopenic purpura (ITP). A 72-year-old man was diagnosed with idiopathic thrombocytopenic purpura (ITP). After receiving 4 cycles of rituximab in one month complete response was achieved. However, three weeks after the last infusion he presented to the haematology department with fever, productive cough and dyspnea and severe hypoxemia. HRCT of the thorax revealed patchy areas of ground glass opacities throughout both lungs and small peripheral consolidations were seen. Transbronchial biopsy showed interstitial thickening and type II pneumocyte activation with interstitial pneumonia. Bronchoalveolar lavage showed increased eosinophils. The patient was treated with three pulses of 1 gr iv methylprednisolone and then gradually switched to 15 mg of prednisolone for 3 months. The dyspnea and tachypnea gradually improved, in addition to blood oxygenation and a follow up HRCT 3 months later showed a significant resolution of lesions.
Severe lung toxicity like acute respiratory distress syndrome, cryptogenic organizing pneumonia, pneumonitis, and interstitial lung disease are very rare, with most of the knowledge coming from case reports. Rituximab-induced interstitial lung disease (R-ILD) is a rare complication. To the best of our knowledge, 23 cases of R-ILD have been reported in the literature; 22 of them were treated with R-CHOP for NHL and only one was receiving rituximab for ITP. We report the second case to develop this complication for a non-malignant disorder.

1. Introduction

Rituximab, a chimeric anti-CD20 IgG1 monoclonal antibody, is an effective treatment for haematological autoimmune diseases such as idiopathic thrombocytopenic purpura (ITP) (Figs 1 and 2).[1–3] Recently, it has become clear that B cells play a key role in both the development and perpetuation of autoimmunity, suggesting that B-cell depletion could be a valuable treatment approach for patients with autoimmune diseases. Rituximab specifically depletes B cells and is widely used today as second line treatment for ITP.[1–3] The most common side effects are infusion related and include fever, chills, and rigours.[4] Respiratory complications can include cough, rhinitis, bronchospasm, dyspnea and sinusitis. Severe lung toxicity like acute respiratory distress syndrome, cryptogenic organizing pneumonia, pneumonitis, and interstitial lung disease are very rare, with most of the knowledge coming from case reports.[5]

2. Case report

A 72-year-old man was diagnosed in march 2008 with idiopathic thrombocytopenic purpura. He initially received high dose corticosteroids with no response. After receiving 4 cycles of rituximab in one month (last one 5th May 2008) complete response was achieved. Three weeks after the last infusion he presented to the haematology department with fever, productive cough and dyspnea and was transferred to our department for further evaluation. On physical evaluation he was tachypnoic and tachycardic. Physical examination revealed bilateral crackles. He was hypoxemic ($PO_2 = 63$ mmHg, FiO_2 MV35%). Pulmonary function tests revealed a mild restrictive pattern with severe reduction in diffusion capacity (DLco = 37.2% pred.) (Table 1). Chest X-ray showed a bilateral hazy reticulonodular pattern in the middle and lower lung fields Empirical broad spectrum antibiotics were

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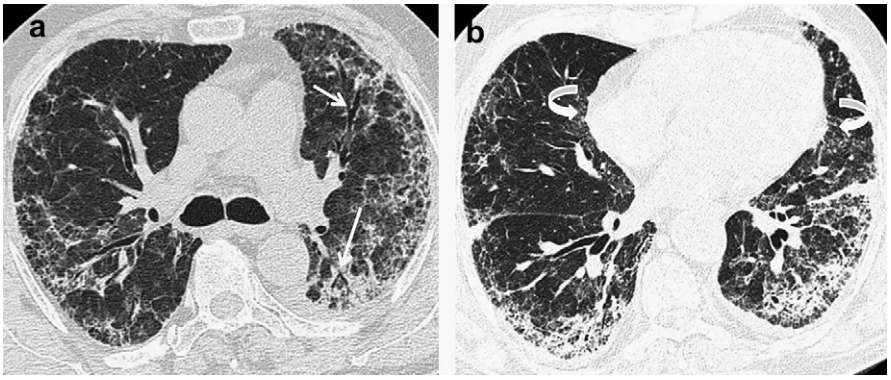

Fig. 1. a, b Initial HRCT in the upper (a) and lower lung fields (b) respectively, shows a reticular pattern of lesions in the peripheral third of both lungs, irregular interfaces and interlobular septa thickening, traction bronchiectasis and bronchiolectasis (arrows) and patchy areas of ground glass attenuation (curved arrows).

started but shortness of breath aggravated. A repeat X-ray 5 days later showed worsening of infiltrates and a HRCT of the thorax was performed. Patchy areas of ground glass opacities throughout both lungs and small peripheral consolidations were seen. A microcystic, reticular pattern of lesions implying intralobular thickening was observed in the peripheral third of both lung fields, more extended in the lower fields. Furthermore, dilated, irregular bronchi and bronchioles compatible with traction bronchectasis/bronchiolectasis, irregular interfaces and interlobular septa pointed to a fibrotic process. Small bilateral pleural effusions were also evident.

The rapid progress of interstitial infiltrates in a previously normal lung as was shown on chest X-rays, and the elements of a fibrotic process revealed by HRCT, pointed to a fibrotic process in the spectrum of nonspecific interstitial pneumonia (NSIP), acute interstitial pneumonia (AIP) on radiological grounds. A bronchoscopy with bronchoalveolar lavage and transbrochial biopsy was performed. Bacterial, viral, *Pneumocystis carinii* (PCP) and fungal cultures were all negative. Transbronchial biopsy showed interstitial thickening and type II pneumocyte activation with interstitial pneumonia. Bronchoalveolar lavage showed increased eosinophils (7%). The patient was treated with three pulses of 1 gr iv methylprednisolone and then gradually switched to 15 mg of prednisolone for 3 months. The dyspnea and tachypnea gradually improved, in addition to blood oxygenation ($PO_2 = 63$ mmHg, $FiO_2 = 21\%$) while chest X-rays gradually improved. A follow up HRCT 3 months later showed a significant resolution of lesions. However, microcystic lesions along with traction bronchiectasis, bronchiolectasis and irregularly thickened interlobular septa remained in the peripheral third of the lungs.

3. Discussion

Current treatment regimens for haematological autoimmune diseases are relatively non-selective and are often associated with considerable toxicity. Recent studies suggest that most patients with immune thrombocytopenic purpura have a disease that is generally well tolerated, with little morbidity. Splenectomy remains the best 'curative' treatment for adults with chronic disease (at least 6 months of follow up). Other treatments such as anti-D, rituximab or dexamethasone may allow the decision of splenectomy to be postponed, possibly indefinitely, if haemostatic platelet count is attained.[1–3]

Adverse pulmonary reactions to rituximab occur as reversible events during the first infusion in 38% of patients. In addition, severe human antibody infusion reactions, generally occurring during the first 2 h of the first infusion, can present with hypotension or angioedema. Pulmonary involvement manifests in the form of bronchospasm, hypoxia, infiltrates and even acute respiratory distress syndrome. Late occurring pulmonary toxicities like cryptogenic organizing pneumonia, pneumonitis, and interstitial lung disease after the administration of rituximab have rarely been reported.[6]

Rituximab induced interstitial lung disease (R-ILD) is a rare complication. 23 cases of R-ILD were found in the literature; 22 of them were treated with R-CHOP for NHL and only one was receiving rituximab for ITP.[8–10]

The almost complete resolution of the HRCT findings in association with clinical improvement and the eosinophilic reaction in bronchoalveolar lavage fluid suggest a drug reaction. The HRCT findings are more consistent with an NSIP like reaction as AIP is

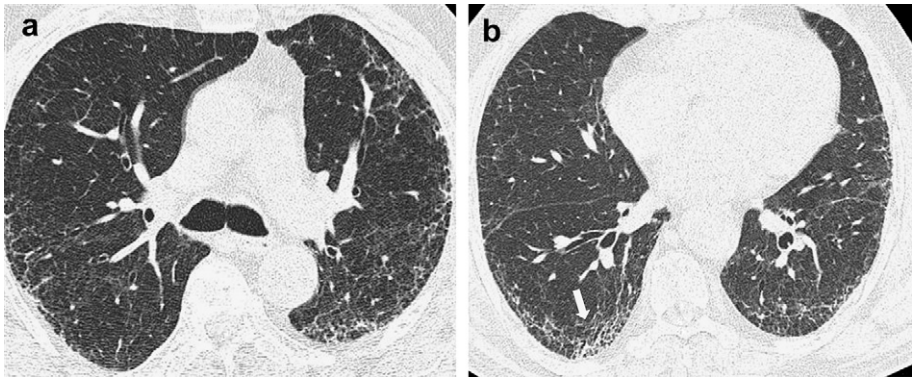

Fig. 2. a, b Follow up HRT at the same levels, shows residual microcystic lesions in the peripheral and dorsal areas as well as traction bronchiolectasis (b, arrow).

Table 1
Pulmonary Function Tests (PFTs) before and after treatment.

Values	Before treatment	3 months after treatment
FEV 1	72.3% pred	96.3% pred
FVC	65.4% pred	86.5% pred
FEV 1/FVC	84.87% pred	85.54% pred
MMEF 75/25	80.1% pred	79.5% pred
TLCOc	37.2% pred	64.1% pred

a fatal disorder and not reversible event and has a specific histopathologic profile of diffuse alveolar damage.

The pathogenesis of R-ILD is largely unknown. The possible pathogenetic mechanisms include the role of complement activation, cytokines, cytotoxic T lymphocytes (CTL) and CD 20 positive T-cells. CTL activation may produce vascular and alveolar damage. Disturbed cellular cytotoxicity can also result from the interaction of rituximab with CD 20 + T-cells or by crossreactivity between lung and tumoral antigens with possible generation of a self reactive clone. Complement activation and cytokine secretion seems to be the causative factors in side effects associated with infusion reactions. In particular, TNF-a has been postulated as the main component in the pathogenesis of ILD because of its proinflammatory effects by inducing chemokines, inflammatory mediators, and angiogenic factors.[7,8]

R-ILD can occur in adult patients who have received rituximab therapy for months. Presenting symptoms include dyspnea, fever, pleuritic pain and cough. Evaluation should include pulse oxymetry and arterial blood gases, a HRCT of the chest and PFTs to determine the pattern of pulmonary disease present. Bronchoscopy with bronchoalveolar lavage should be done to rule out an infectious etiology and biopsy can demonstrate interstitial fibrosis.

The emergence of pulmonary infiltrates in patients treated with rituximab remains a difficult diagnostic problem. Many differential diagnoses need to be considered, including disease progression, infection, cardiogenic edema, radiation pneumonitis, pulmonary hemorrhage, and allergies. One of the major clinical challenges in these patients is ruling out opportunistic infection. The infectious etiologies of diffuse interstitial infiltrates in the lungs are multiple.[9] They include any Gram-negative or Gram-positive agents, fungi (*Aspergillus*, *Candida*), parasites (*P. carinii*, *Toxoplasma gondii*), or viruses (Herpes simplex, Varicella zoster, *Cytomegalovirus*).[9]

Therapy must include corticosteroids, immediate discontinuation of rituximab, and any other clinically necessary measures such as mechanical ventilation. Of the 23 patients treated as mentioned above, 15 lived and 8 of them died. These data suggest that R-ILD is a rare but fatal pulmonary toxicity and the physicians must maintain a high index of suspicion to recognize this complication early.

Conflict of interest statement

The authors declare that this report is original and do not have any conflict of interest.

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